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ABSTRACT

Because breast milk contains small quantities of thyroid hormones not found in commercial formula preparations, it was hypothesized that breast feeding may provide some protective benefit to the hypothyroid infant before medical treatment is begun. Of 108 children with congenital hypothyroidism, breast-fed children had higher thyroid hormone levels than formula-fed children at 1 and 2 months of age, but not later. The intellectual characteristics of the children were evaluated at 1, 3, 5, and 6 years of age. Breast-fed children scored higher in social and fine motor development at 1 year of age and in verbal learning at age 5, when controlling for parent intelligence quotient, socioeconomic status, and hormone dose level. Children with ectopic glands showed the largest benefit of breast feeding, particularly at age 3. These results signify a small protective benefit of breast feeding. (37 references) (JDD)

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DOES BREAST FEEDING PROTECT THE HYPOTHYROID
INFANT DIAGNOSED BY NEWBORN SCREENING?

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ABSTRACT

The intellectual characteristics at 1, 3, 5 and 6 years of age were evaluated in 108 congenital hypothyroid children who had either been breast-fed (BF) or formula-fed (FF) in infancy. BF had higher T_4 levels than FF ($p < .001$) at 1 and 2 months of age, but not later. Controlling for parent IQ, SES, and dose level, we found that BF scored higher in social and fine motor development at 12 months of age and in verbal learning at age 5. Children with ectopic glands showed the largest benefit of breast feeding, particularly at age 3. These results signify a small, presumably protective, ~~in~~ benefit of breast feeding.

DOES BREAST FEEDING PROTECT THE HYPOTHYROID
INFANT DIAGNOSED BY NEWBORN SCREENING?

Screening newborns for congenital hypothyroidism (CH) allows for earlier hormone replacement than was previously possible with clinical diagnosis. However, even with fastest of screening programs, there is still a delay before treatment is initiated and euthyroidism achieved. This delay may be ^{later} associated ^{with} ~~later~~ neurocognitive impairment (1-4). Because breast milk contains small quantities of thyroid hormones not found in commercial formula preparations (5-9), breast feeding may provide some protective benefit to the hypothyroid infant before treatment can be given, and euthyroidism ultimately achieved (10). Indeed several cases have been described with congenital hypothyroidism that only became clinically evident once breast feeding was discontinued (11). Furthermore, a retrospective study involving 51 9 to 15 year old ~~4~~ children with CH diagnosed clinically found that breast feeding in infancy was associated with better intellectual prognosis than ~~was~~ formula feeding (12). Also because higher IQs were associated with earlier treatment onset in ~~the~~ formula-fed (FF) group, but not the breast-fed (BF) ^{children,} ^{this was} ^A thought to indicate the ~~breast-fed~~ ^{BF} were receiving some protection prior to being treated (12).

The evidence on children diagnosed by newborn screening is less optimistic but the issue has not as yet been adequately resolved. Letarte et al (13) reported no difference between 12 BF and 33 FF CH children at one year of age in their growth or intellectual outcome. We similarly reported no difference in intelligence between 30 BF and 31 FF CH children who ranged from 1 to 6 years of age, with the majority below age 2 (14). However, both of these

studies were limited methodologically by their relatively small sample sizes and the very young ages of the samples, when instruments used to assess intelligence are generally less valid and relatively poorer predictors of outcome. Moreover, few if any deficits have even been reported in CH children at these young ages (3). Both studies also failed to control for such factors as socioeconomic status (SES) and parental intelligence, which influence choice of feeding method and intellectual outcome (15,16), as well as etiology of the hypothyroidism. X

We presently report our findings on larger groups of BF and FF CH children as infants and at ages when impairments in neurocognitive function have been shown to occur (17). It is hypothesized that if breast milk is ^oprotective: (i) BF should perform better than FF when family variables (SES and parent IQ) are controlled; (ii) the differences between BF and FF should be greater at older than at younger ages; (iii) the differences should be larger in children who are missing their thyroid gland than children with partial thyroid function; and (iv) the correlation between outcome and delay in treatment onset should be greater in FF than BF.

SUBJECTS AND METHODS

The sample consisted of 109 hypothyroid children (33 males) diagnosed by neonatal screening in Toronto (18,19). Sample characteristics have been described elsewhere (18,20). Thirty-two children had athyrosis, 29 dysmorphogenesis usually with goitre, and 48, ectopic glands.

These children represent a cohort that was born between 1976 and 1986 and which has been participating in an ongoing prospective study since 1981 to evaluate outcome in screened CH patients. This cohort represents 95% of all

cases with hypothyroidism being managed at our hospital. In this study, children are routinely assessed on an annual basis throughout childhood. Sixty-eight children entered the project at the age of 12 months, while the remainder, who were above this age when the study began, were first seen at their next birthday (13 at 2 years, 12 at 3 years, 6 at 4 years, 7 at 5 years, and 3 at 6 years). Assessments were conducted at The Hospital for Sick Children by psychometrists who were blind to feeding status. Testing of one parent (usually mother) took place at the child's initial assessment. Sixty-eight (45 BF) children were assessed at one year, 84 (at (54 BF) 3 years, 69 (32 BF) at 5 years, and 67 (29 BF) at 6 years.

The test measures for the child's one year assessment included the Griffiths (21) and Reynell Language Scales (22); for the three year assessment, the Griffiths, Reynell, and Beery (23); for the five year assessment, the WPPSI (24), Beery, Reynell, and McCarthy Memory and Motor scales (25); and for the six year assessment, the McCarthy, Reynell, Beery, and Bruininks (26). Parent IQ was assessed with the abbreviated WAIS-R (27) and SES with the Hollingshead (28). At the initial assessment, all parents were interviewed about feeding method and age at discontinuing breast feeding.

The following information was obtained from the medical charts: age at treatment onset; starting dosage; and TSH, T_4 , and T_3 levels at diagnosis and at clinic visits throughout the first year. This usually involved monthly visits until 4 months, then at 6, 9, and 12 months, and annually thereafter. Age of normalization of thyroxine was determined by extrapolating from the regression between hormone levels and age for each child, when the circulating T_4 level would have reached 10.0 $\mu\text{g/dL}$ (see 29 for rationale).

The data were analyzed by multivariate t-tests (one-tailed) and multivariate analyses of covariance (MANCOVA). Pearson correlations were used to determine the relationships of treatment age with outcome.

The study was approved by The Hospital for Sick Children's Human Subjects Review Committee.

RESULTS

Sixty-two (57%) CH were breast-fed while 46 were formula fed; feeding status was not available on one child. Mean (SD) duration of breast feeding was 19.5 (149) weeks (range: 2 wks to 1 yr).

BF did not differ from FF on any factor associated with illness severity. Their mean skeletal ages at diagnosis were 36.6 wks for BF and 37.0 for FF. Screening and confirmation TSH levels were 119.3 μ U/dL and 129.5 μ U/dL for BF and 133.0 μ U/dL and 135.6 μ U/dL for FF. The distribution of BF in each of the etiological categories was 67% for athyrotics, 42% for goiters and 57% for ectopics. Regarding treatment, the mean (SD) age at initiating replacement therapy was 13.9 (5.8) days for BF and 13.0 (6.4) for FF. Their mean (SD) daily starting dosages were 8.22 (1.7) μ g/kg and 7.48 (1.9) μ g/kg respectively, which is significantly different ($p < .03$). Parental IQ was higher for BF ($p < .01$), as was SES ($p < .01$). X

BF had significantly ($p < .001$) higher T_4 levels than FF at 1 and 2 months of age, but not past this age (see Table 1). T_4 appeared to be normalized for BF by 1 month of age, which is within two weeks of starting therapy. For FF, however, this did not occur until two months of age for children with goiter and ectopic glands, and until three months for children with athyrosis (Figure 1). It took 27.5 days on average for the T_4 levels of BF children to reach 10.0 μ g/dL compared with 70.8 days for FF, which is

significantly different ($p < .01$). All groups had T_3 levels within the normal range (30) by one month of age, except infants with athyrosis who were formula-fed.

Insert Table 1 and Figure 1 about here

Because starting dose level, parent IQ, and SES differed for BF and FF groups, these variables were used as covariates in all subsequent analyses. The MANCOVA test revealed no overall difference at any age between BF and FF children. Univariate tests showed a significant advantage of breast feeding at one year of age on two Griffiths subscales, Personal Social ($F = 4.43$, $p < .05$; $df = 1,61$) and Eye-Hand Coordination, ($F = 4.31$, $p < .05$; $df = 1,61$) and at age 5 on the WPPSI Similarities subtest, which measures verbal reasoning abilities ($F = 3.77$, $p < .05$, $df = 1,50$). The mean scores for these measures are given in Table 2. There were no differences between BF and FF at the 3 or 6 year assessments or in other areas of mental functioning.

Insert Table 2 about here

We examined the effects of breast feeding according to etiology of hypothyroidism by using a series of 2 (feed) x 3 (etiology) MANCOVAs. A significant group x feed interaction was found for the three year assessment data ($F(14,497) = 2.19$, $P < .01$). As can be seen in Figure 2, children with ectopic glands who were breast-fed obtained the highest scores, which are comparable to the levels of normal controls described previously (4).

However, ^{among} ~~formula-fed~~ children with ectopic ^{FF} glands scored similar to ^{all} children with athyrosis. They differed from BF on Personal Social ($p < .04$) and Eye Coordination ($p < .01$) scales at one year of age and on Locomotion skills ($p < .04$), Personal Social ($p < .02$), and Reasoning ($p < .01$) at age 3. There ^{no} were comparable effects for the tests given at 5 and 6 years of age. [^]

Insert Figure 2 about here

Hypothesis four predicted that if breast feeding is protective, negative correlations would be observed between outcome variables and age at treatment onset for FF but not BF; the difference between the two groups' correlation coefficients should also be significant. This pattern of results was observed for Eye-Hand Coordination skills at 12 months of age ($r = -.078$ for BF and $-.612$, $p < .001$ for FF) and for Neuromotor skills as assessed by the Bruinicks at age 6 ($r = .092$ and $-.341$, $p < .05$).

DISCUSSION

The results revealed that children with CH who received breast milk in early infancy had higher T_4 levels in the first two months of life and achieved euthyroidism sooner than did children who were given commercial formula preparations. On intellectual testing, the breast-fed group demonstrated advantages in fine motor skills and social development as infants and in verbal reasoning at age 5, thereby providing some, albeit minimal, support for the first two hypotheses.

It was also predicted that the children with the athyrotic condition should benefit most from breast feeding because they had the most severe

conditions and the lowest thyroid hormone levels. Present findings, however, showed an advantage of breast feeding only for children with ectopic glands, This was observed primarily at 1 and 3 years of age and in several areas of intellectual functioning. Because the ectopic etiology is usually associated with partial thyroid function, this result seems initially counterintuitive. However, recent studies suggest that the ectopic condition is not static but ^{is} rather on a continuum with the athyrotic etiology, with the ectopic progressively losing functional capacity after birth (31). It is possible that supplementary thyroxine in breast milk is adequate for these children as their residues vanish but is insufficient for the children who lack thyroid glands. Furthermore, the protective benefit may be too late for these ^{with athyrosis} children because their cognitive deficits appear to be prenatal in origin (32).

There was also some support for the fourth hypothesis that if breast feeding is beneficial, outcome would be negatively associated with the delay in treatment onset for FF but not BF children because the latter are being protected during this period. This was observed for fine motor skills on the one year assessment and overall neuromotor competence on the six year assessment.

It is not readily clear what the protective mechanism of breast feeding actually is. Studies of the hormonal constituents of breast milk report low but persistent levels of T_3 , which only become evident after 1 month of age, but non-detectable levels of T_4 (8,33). Furthermore, it is not certain what the effects can be when the levels of T_3 in breast milk only amount to what represent 25% of the total daily requirement (5,8). Nevertheless, one might argue that it is not the total amount of hormone that is important ^{but} the [^] timing of its presence at a critical stage of neural maturation that is essential.

Besides the benefits from exogenous thyroid hormones in breast milk, this method of feeding has also been shown to impact positively and over the long-term on the neurocognitive skills of normal healthy non-hypothyroid children (13,33,34). There is some thought that this is due to psychological effects as well as other to metabolites ~~also~~ unique to breast milk. However, ^X because we did not record the method of feeding in our controls, we have no way of knowing whether the benefits observed presently were due to thyroid hormones in the milk or to these other psychological and metabolic ^{effects} ~~benefits~~. By the same token, one also does not know what produced the advantages reported in the other studies on healthy breast-fed children (13) because they did not assay for thyroxine or other metabolites. Clearly further studies in this area are necessary.

Other limitations of the present work ^{also} include (i) our inability to control for daily fluctuations in hormone levels; (ii) individual sensitivities; (iii) compliance; (iv) incomplete ingestion of administered T_4 ; (v) variations in function of the ectopic group; and (vi) the reliability of test measures, particularly the infant tests. Unfortunately, ^{as} the first five factors are different to control, ^{minimal because they are} one has to assume that their effects are randomly distributed throughout both feeding groups. Furthermore, among infant tests, the Griffiths is considered one of the more sensitive and widely used in this type of research, although its current norms are relatively inflated (36,37).

In conclusion, this study has provided some partial support for the hypothesis that breast feeding will protect the hypothyroid infant. It appears that breastfeeding is associated with better social and fine motor skill development in early childhood and with better verbal skills later, particularly if the child has the ectopic condition. For pediatricians, ^{the}

~~practical implications of present findings~~ ^{are that they should} ~~suggest the need for~~ encouraging
mothers of hypothyroid children who do choose to breast feed, to continue as
long as possible, at least until hormone levels have normalized, ^{and} especially if
the child has a gland that is ectopic.

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FIGURE CAPTION

Figure 1. Mean Thyroid Hormone Levels in Early Infancy of BF and FF Children According to Etiology of Hypothyroidism A. T_4 ; B. T_3 .

Note: Values plotted at each monthly interval do not represent complete cohort as not all of the children followed exactly the prescribed medical protocol (see Subjects and Methods).

Figure 2. Griffiths GQ Scores of BF and FF Children at Age 3 by Etiology of Hypothyroidism.

Table 1
Mean (SEM) T_4 and T_3 Levels of Breast Fed (BF)
and Formula Fed (FF) CH Children

	T_4 ($\mu\text{g/dL}$)		T_3 ($\mu\text{g/dL}$)	
	BF	FF	BF	FF
Diagnosis	4.9 (.27)	5.7 (.29)	129.5 (10.5)	145.8 (10.9)
1 Month	12.5 (.73)	8.6 (.73)*	175.7 (13.0)	197.3 (15.6)
2 Months	13.2 (.61)	10.0 (.62)*	171.8 (9.8)	231.1 (12.4)
3 Months	13.2 (.58)	12.1 (.59)	193.9 (9.1)	208.3 (16.3)
4 Months	13.7 (.59)	13.5 (.64)	207.0 (11.7)	194.6 (11.7)
6 Months	13.5 (1.0)	13.2 (.49)	193.3 (8.5)	196.0 (9.1)
9 Months	12.7 (.76)	12.0 (.49)	180.5 (7.2)	202.5 (11.7)
12 Months	12.5 (.40)	13.4 (.35)	191.4 (11.7)	184.2 (5.7)

* $p < .001$

Table 2

Mean $\pm$ SD Scores on Tests Where BF Scored Higher than FF

	BF	FF
<u>1 Year</u>		
N	39	23
Personal Social	111.8 $\pm$ 12.9	105.6 $\pm$ 10.7
Eye Hand Coordination	113.5 $\pm$ 9.3	107.0 $\pm$ 7.3
<u>5 Years</u>		
N	31	24
Similarities	12.3 $\pm$ 3.1	10.5 $\pm$ 2.8

Table 2

Mean $\pm$ SD Scores on Tests Where BF Scored Higher than FF

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<u>1 Year</u>		
N	39	23
Personal Social	111.8 $\pm$ 12.9	105.6 $\pm$ 10.7
Eye Hand Coordination	113.5 $\pm$ 9.3	107.0 $\pm$ 7.3
<u>5 Years</u>		
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